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EXHIBIT C

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of inventors Ketner et al.

Serial No. 09/904,698

Group Art Unit: 4755

Filed: 07/13/01

Examiner: Hill

For: ***“USE OF GENE PRODUCT OF ADENOVIRUS EARLY REGION 4 ORF-6 TO
INHIBIT REPAIR OF DOUBLE-STRAND BREAKS IN DNA”***

Mail Stop Non-Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT UNDER 37 C.F.R. §1.111

Sir:

In response to the Office Action mailed on 02/11/2003, please amend the above-identified patent application as follows:

Amendments to the Claims are indicated by the notation “currently amended”, “withdrawn” “cancelled” or “original” in the listing of claims beginning on page 2 of this paper.

Remarks begin on page 5 of this paper.

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IN THE CLAIMS:

What is claimed is:

1-5. (Cancelled)

6. (Currently amended) A method of inhibiting repair of double stranded breaks in ~~double stranded~~ DNA in a cell which comprises introducing into the cell ~~the gene product of the~~ DNA containing early region 4 (E4) open reading frame 6 (ORF-6) and E1B region of genomic adenoviral DNA.

7. (Withdrawn) A method of preventing cancer in a subject which comprises introducing into a cell of the subject the gene product of the early region 4 (E4) open reading frame 6 (ORF-6) of genomic adenoviral DNA.

8. (Withdrawn) A method of treating cancer in a subject which comprises introducing into a cancer cell of the subject the gene product of the early region 4 (E4) open reading frame 6 (ORF-6) of genomic adenoviral DNA.

9. (Withdrawn) A method of preventing concatamerization of a linear wild-type adenoviral DNA which comprises introducing into a cell comprising the wild-type adenoviral DNA, the gene product of the early region 4 (E4) open reading frame 6 (ORF-6) of genomic adenoviral DNA.

10. (Withdrawn) A method of inhibiting V(D)J recombination of nucleic acid sequences encoding immunoglobulins in a cell of the immune system which comprises introducing into the cell, the gene product of the early region 4 (E4) open reading frame 6 (ORF-6) of genomic adenoviral DNA.

11. (Withdrawn) A method of preventing in a cell apoptosis induced by viral DNA replication in

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the cell which comprises introducing into the cell, the gene product of the early region 4 (E4) open reading frame 6 (ORF-6) of genomic adenoviral DNA.

12. (Currently amended) A method ~~of increasing efficiency of~~ for chemotherapeutic or radiation treatment of cancer in a subject while inhibiting repair of double-stranded breaks in DNA in cancer cells in said subject which comprises: a) introducing into said cancer cells ~~of the subject~~ the gene product of the DNA containing early region 4 (E4) open reading frame 6 (ORF-6) and E1B region of genomic adenoviral DNA in a quantity sufficient to inhibit repair of double-stranded breaks in DNA in said cancer cells and b) administering a chemotherapeutic agent or radiation to the subject.

13. (Currently amended) The method of claim 12, wherein the ~~gene product of the~~ DNA containing early region 4 (E4) open reading frame 6 (ORF-6) and E1B region of genomic adenoviral DNA is introduced into the cancer cells before the chemotherapeutic agent or radiation is administered to the subject.

14. (Currently amended) The method of claim 12, wherein the ~~gene product of the~~ DNA containing early region 4 (E4) open reading frame 6 (ORF-6) and E1B region of genomic adenoviral DNA is introduced into the cancer cells after the chemotherapeutic agent or radiation is administered to the subject.

15. (Currently amended) The method of claim 12, wherein the ~~gene product of the~~ DNA containing early region 4 (E4) open reading frame 6 (ORF-6) and E1B region of genomic adenoviral DNA is introduced into the cancer cells concurrently with administering the chemotherapeutic agent or radiation to the subject.

16. (Original) The method of claim 12, wherein the chemotherapeutic agent is cisplatin or doxorubicin.

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17. (Withdrawn) The method of claim 6 wherein said step of introducing is performed by transfection.

18. (Withdrawn) The method of claim 11 wherein said step of introducing is performed by transfection.

REMARKS

Claims 6-18 are pending in the application. Claims 6 and 12-16 are under consideration, claims 7-11, 17 and 18 having been withdrawn from consideration as the result of a restriction requirement. By this amendment, claims 6 and 12-15 have been amended.

35 U.S.C. § 112, second paragraph rejection

Claims 6 and 12-16 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Examiner states that it is not clear in the method what is being introduced into the cell or what is intended to be introduced into the cell, the gene (nucleic acid) or the gene product (protein). For the present Office Action, the Examiner has assumed that the gene is introduced and the gene product expressed from the gene *in vivo*.

Claims 6 and 12-15 have hereby been amended to recite that it is DNA containing the relevant encoding sequences that is introduced into the cell. Applicant submits that this amendment does not introduce new matter since, for example, on page 25 at lines 33-36 of the specification two exemplary methods of introducing the gene product are given (via a plasmid and via an adenoviral vector), both of which involve introducing DNA into the cell.

Claim 6 has further been amended to recite that it is the “repair of double-stranded breaks in DNA” that is corrected rather than the “repair of breaks in double-stranded DNA”. Applicant submits that other types of breaks can occur in double-stranded DNA (e.g. single strand breaks) but that the subject matter of the present invention is accurately described as the repair of double-stranded breaks in DNA. The previous error was inadvertently introduced in the last amendment to claim 6. Support for the present form of claim 6 is found in the specification, for example, at page 22, lines 10-11. Thus, this amendment does not introduce new matter.

Examiner further asserts that it is not clear in claims 12-16 what is meant by “increasing efficiency” of the agent.

Claim 12 has hereby been amended to eliminate the phrase “increasing efficiency”. Claim

12 has been amended to recite that the method is a method for chemotherapeutic or radiation treatment of cancer in a subject while inhibiting repair of breaks in double strand DNA in cancer cells in the subject. Support for the claim is found in the specification, for example on page 43, lines 8-12. Radiation and chemotherapy treatments are known to induce double strand breaks in cellular DNA, resulting in cell death, unless repair of the breaks occurs. The agent of the present invention has been shown to prevent repair of double strand breaks in cells (see, for example, page 43, lines 27-30; page 76, lines 19-21). Thus, the amendments do not constitute new matter.

35 U.S.C. § 112, first paragraph rejection

Claims 12-16 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Examiner states that chemotherapeutic agents and radiation therapies are a very unpredictable area, that the method would require targeting of the cancer cells, and that, due to the wide range of cancers, the unpredictability in the art, and the lack of specific examples, it would require undue experimentation to use the invention as claimed.

Applicant respectfully disagrees. Examiner has recognized the description of the method of claims 12-16 in the paragraph on page 42, beginning at line 29. Applicant submits that the paragraph, in conjunction with knowledge extant in the field, gives ample guidance for the use of the adenoviral vector of the present invention for increasing efficiency of chemotherapeutic or radiation treatment of cancer cells, via inhibiting the repair of double-stranded breaks in DNA in the cancer cells.

Applicant submits that the field of gene therapy has progressed significantly and that a body of literature which provides guidance to those in the field exists. Skilled artisans, such as physicians experienced in gene therapy, would recognize that the delivery of genetic material via adenoviruses to cells in general, and to cancer cells in particular, is well-known, and will be aware of the various alternatives available for carrying out delivery of the adenovirus. For example, Khuri et al. and Schuler et al. (described above) both describe the use of adenoviral vectors in conjunction with radiation or chemotherapy to improve the results of the cancer

therapy. Further, modifications to an adenoviral vector such as those described in the present invention would not interfere with delivery of the adenovirus or the pattern of gene expression described in amended claims 6 and 12, as many versions of adenoviral vectors are known and have been successfully used to transfect cells *in vivo*.

The “experimental” aspect of the present invention is the discovery of which genes are beneficial to express for the purpose of inhibiting the repair of double-stranded breaks in DNA. Thus, one skilled in the art would require no more explicit teaching than that which is found in the present application, coupled with the knowledge in the field at the time the present application was filed, in order to successfully practice the present invention as recited in claims 12-16.

In view of the foregoing, reconsideration and withdrawal of this rejection are respectfully requested.

35 U.S.C. §102 (b) rejection

Claim 6 stands rejected under 35 U.S.C. §102 (b) as anticipated by Ramalingam et al.. Examiner states that Ramalingam et al. discloses an adenovirus that expresses E4 orf 6 (column 2, second full paragraph). Examiner states that while Ramalingam is silent on the effect of E4ORF6, the method involves the same step of introducing into the cell the gene product of E4ORF6 by way of adenovirus infection.

Claim 6 has hereby been amended to recite that both E4 orf6 and region E1B of the adenoviral genome are introduced into a cell in order to inhibit repair of double-stranded breaks in DNA in the cell. Support for this amendment is found in the specification at page 21, lines 16-19, and on page 25, lines 17-19, both of which locations state that in some embodiments of the invention, both E4 orf6 and region E1B are utilized. Applicant submits that this amendment therefore does not introduce new matter.

Ramalingam et al. utilize adenoviral gene transfer vectors in which the E4 region is present but in which the E1 region is absent. Therefore, the work described by Ramalingam et al. does not anticipate claim 6 as amended, which requires the presence of both E4 orf6 and region E1B.

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In view of the foregoing, reconsideration and withdrawal of this rejection are respectfully requested.

35 U.S.C. §102 (a) rejection

Claims 6 and 12-16 stand rejected under 35 U.S.C. §102 (a) as anticipated by Vollmer. Examiner states that Vollmer discloses a method of improving the efficiency of chemotherapeutic agents with adenovirus E4 orf 6 in mice, and that while Vollmer is silent on E4 orf 6, the virus was grown on 293 cells which only complement E1 mutant adenoviruses and therefore the virus must have E4 orf 6.

Claim 6 has hereby been amended to recite that both E4 orf6 and region E1B of the adenoviral genome are introduced into a cell in order to inhibit repair of double-stranded breaks in DNA in the cell. Claim 12 has hereby been amended to recite that both E4 orf6 and region E1B of the adenoviral genome are introduced into a cancer cell in order to inhibit repair of double-stranded breaks in DNA in the cell caused by chemo- or radiation therapy. Support for these amendments is as discussed above. The work of Vollmer et al. was carried out with a construct containing all of the adenoviral genome except E1B. Therefore, Vollmer et al. do not anticipate the subject matter of claims 6 and 12 (and thus dependent claims 13-16) as amended since claims 6 and 12 now recite the presence of both E4 orf6 and region E1B.

In view of the foregoing, reconsideration and withdrawal of this rejection are respectfully requested.

Formal Matters and Conclusion

In view of the foregoing, Applicant submits that all rejections have been successfully traversed. The Examiner is respectfully requested to pass the above application to issue at the earliest possible time.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at the local telephone number listed below to discuss any other changes deemed necessary in a telephonic or personal interview.

Please charge any underpayment or credit any overpayment of fees to attorney's deposit account # 50-2041.

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Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Ruth E. Tyler-Cross', with a large, stylized flourish extending from the end.

Ruth E. Tyler-Cross

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